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L3 fluticasone	2

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DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=AND			
L4	L3 fluticasone	2	L4
L3	L1 monohydrate	6	L3
L2	L1 propellant-free	3	L2
L1	tiotropium (aerosol or inhaler) steroid solvent	18	L1

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Physicians' Desk Reference

PRODUCT NAME

Brands/Generics found for search string: **tiotropium**

None were found.

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PDR® entry for

DUONEB™ (Dey)
(Ipratropium Bromide 0.5 mg/Albuterol Sulfate 3.0 mg*)

INHALATION SOLUTION
*Equivalent to 2.5 mg albuterol base

Description

DESCRIPTION

The active components in DuoNeb™ Inhalation Solution are albuterol sulfate and ipratropium bromide.

Albuterol sulfate, is a salt of racemic albuterol and a relatively selective (beta) $_2$ -adrenergic bronchodilator chemically described as (alpha) ^{1} -[(tert-butylamino)methyl]-4-hydroxy-m-xylene-(alpha), (alpha)'-diol sulfate (2:1) (salt). It has a molecular weight of 576.7 and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. It is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization recommended name for albuterol base is salbutamol.

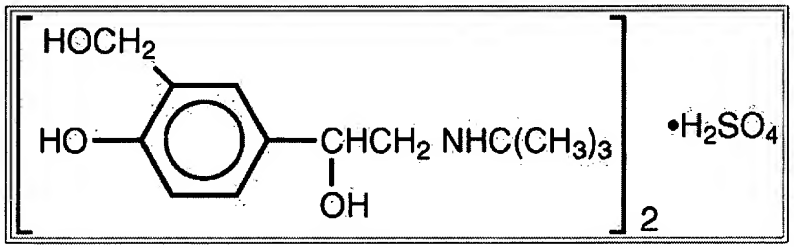

Figure 3.1-1. Chemical structure of albuterol sulfate.

Ipratropium bromide is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo [3.2.1]-octane, 3-(3- hydroxy-1-oxo-2-phenylpropoxy)-8methyl-8-(1-methylethyl)-, bromide, monohydrate (endo, syn)-, (±)-; a synthetic quaternary ammonium compound, chemically related to atropine. It has a molecular weight of 430.4 and the empirical formula is $C_{20}H_{30}BrNO_3 \cdot H_2O$. It is a white crystalline substance, freely soluble in water and lower alcohols, and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

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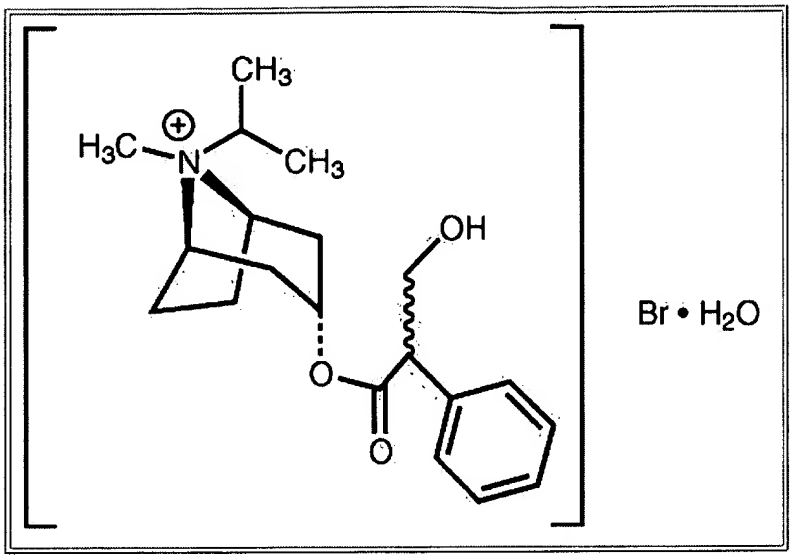

Figure 3.1-2. Chemical structure of ipratropium bromide.

Each 3 mL vial of DuoNeb contains 3.0 mg (0.1%) of albuterol sulfate (equivalent to 2.5 mg (0.083%) of albuterol base) and 0.5 mg (0.017%) of ipratropium bromide in an isotonic, sterile, aqueous solution containing sodium chloride, hydrochloric acid to adjust to pH 4, and edetate disodium, USP (a chelating agent).

DuoNeb is a clear, colorless solution. It does not require dilution prior to administration by nebulization. For DuoNeb Inhalation Solution, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONEB™ compressor system, under in vitro conditions, the mean delivered dose from the mouth piece (% nominal dose) was approximately 46% of albuterol and 42% of ipraropium bromide at a mean flow rate of 3.6 L/min. The mean nebulization time was 15 minutes or less. DuoNeb should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

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CLINICAL PHARMACOLOGY

DuoNeb Inhalation Solution is a combination of the (beta) $_2$ -adrenergic bronchodilator, albuterol sulfate, and the cholinergic bronchodilator, ipratropium bromide.

Albuterol sulfate

Mechanism of Action. The prime action of (beta)-adrenergic drugs is to stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The cAMP thus formed mediates the cellular responses. In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on (beta) $_2$ -adrenergic receptors compared with isoproterenol. While it is recognized that (beta) $_2$ -adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicated that 10% to 50% of the (beta)-receptors in the human heart may be (beta) $_2$ -receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more

effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other (beta)-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients.

Pharmacokinetics: Albuterol sulfate is longer acting than isoproterenol in most patients by any route of administration, because it is not a substrate for the cellular uptake processes for catecholamine nor for the metabolism of catechol-O-methyl transferase. Instead the drug is conjugatively metabolized to albuterol 4'-O-sulfate.

Animal Pharmacology/Toxicology: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of plasma concentrations. In structures outside of the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those found in whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methyl-xanthines are administered concurrently. The clinical significance of these findings is unknown.

Ipratropium bromide

Mechanism of Action: Ipratropium bromide is an anticholinergic (parasympatholytic) agent, which blocks the muscarinic receptors of acetylcholine, and, based on animal studies, appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cGMP), resulting from the interaction of acetylcholine with the muscarinic receptors of bronchial smooth muscle.

Pharmacokinetics: The bronchodilation following inhalation of ipratropium is primarily a local, site-specific effect, not a systemic one. Much of an inhaled dose is swallowed as shown by fecal excretion studies. Following nebulization of a 1-mg dose to healthy volunteers, a mean of 4% of the dose was excreted unchanged in the urine.

Information for Patients

The action of DuoNeb should last up to 5 hours. DuoNeb should not be used more frequently than recommended. Patients should be instructed not to increase the dose or frequency of DuoNeb without consulting their healthcare provider. If symptoms worsen, patients should be instructed to seek medical consultation.

Patients must avoid exposing their eyes to this product as temporary papillary dilation, blurred vision, eye pain, or precipitation or worsening of narrow-angle glaucoma may occur, and therefore proper nebulizer technique should be assured, particularly if a mask is used.

If a patient becomes pregnant or begins nursing while on DuoNeb, they should contact their healthcare provider about use of DuoNeb.

See the illustrated Patient's Instruction for Use in the product package insert.

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Drug Interactions

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is, therefore, advised in the co-administration of DuoNeb with other drugs having anticholinergic properties.

(beta)-adrenergic agents: Caution is advised in the co-administration of DuoNeb and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

(beta)-receptor blocking agents: These agents and albuterol sulfate inhibit the effect of each other. (beta)-receptor blocking agents should be used with caution in patients with hyperreactive airways, and if used, relatively selective (beta) $_1$ selective agents are recommended.

Diuretics: The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by (beta)-agonists, especially when the recommended dose of the (beta)-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of (beta)-agonist-containing drugs, such as DuoNeb, with non-potassium sparing diuretics.

Monoamine oxidase inhibitors or tricyclic antidepressants: DuoNeb should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents because the action of albuterol sulfate on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Albuterol Sulfate: In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m ^{2} basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m ^{2} basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 20 times the maximum recommended daily inhalation dose for adults on a mg/m ^{2} basis). Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleous assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m ^{2} basis).

Ipratropium bromide: In 2-year studies in Sprague-Dawley rats and CD-1 mice, ipratropium bromide showed no evidence of tumorigenicity at oral doses up to 6 mg/kg (approximately 15 times and 8 times the maximum recommended daily inhalation dose for adults in rats and mice respectively, on a mg/m ^{2} basis).